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ES&T SERIES

Cancer dose-response extrapolations

Third of a five-part series on cancer risk assessment

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Quantitative dose-response modeling is an important contributor to cancer risk assessment; hence, it is a major factor in cancer risk management and the regulatory process. The dose-response models now used in the regulatory process are overly simplistic, probabilistic representations of highly complex biological phenomena; these models are not biological models. Several of these simplistic models provide similar fits to the high-dose data generated in chronic animal bioassays but provide dissimilar projections of risk at the lower doses of interest to man. Figure 1 shows model extrapolations.

The possibilities for the low-dose behavior of a simplistic model can be so independent of the fit of that model to the experimental data that an upper confidence limit, or upper bound, on the risk at a low dose can be orders of magnitude larger than the fitted model value. Figure 2 shows that the upper bounds are not responsive to the experimental data, and Figure 3 shows that experimental outcomes with vastly different observed dose-response patterns all have essentially the same upper bounds.

The potency measures, such as unit risks and relative risks, cited by the regulatory agencies are based on upper bounds and not on fitted model values. These measurements do not differentiate between carcinogens on the basis of available experimental data about the shapes of the dose-response relationship. The inability to differentiate between risks is a serious shortcoming when all alternatives involve some risk.

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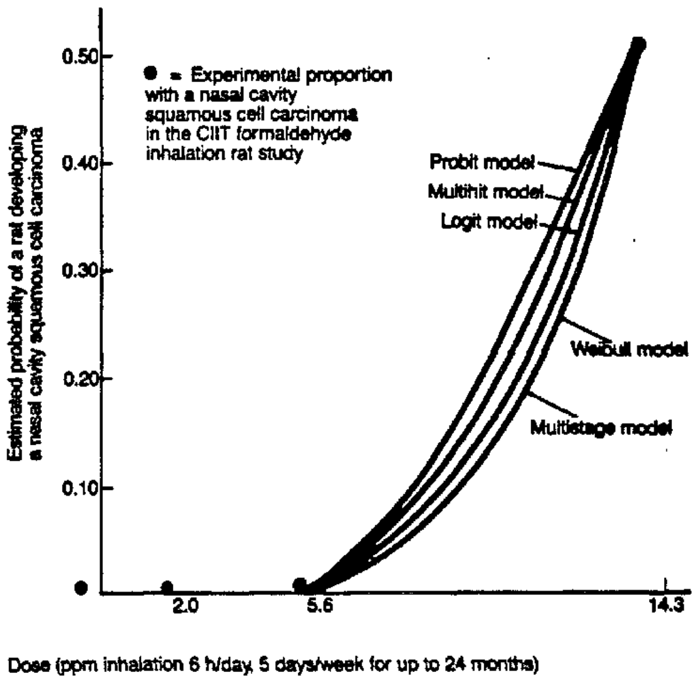
FIGURE 1

Five simplistic models with similar fits to the high dose experimental data . . .[a,b]

. . . Similar fits at higher experiment doses



. . . Dissimilar predictions at lower doses

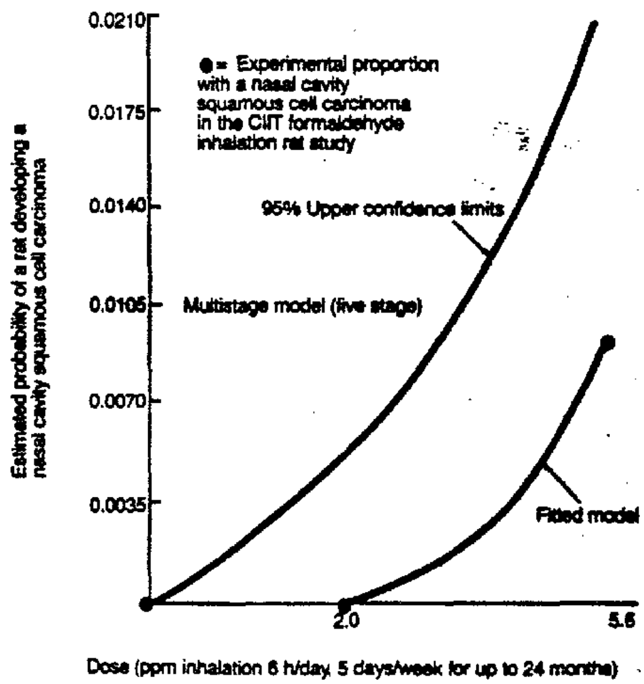
Dose (ppm)	Ratio = Risk estimated using fitted multistage model / Risk estimated using fitted probit model
5.6	1.0
5.0	1.3
4.0	3.0
3.0	13.3
2.0	260.0
1.0	300,000.0
0.5	1,600,000,000.0

[a]The multistage model is usually used by EPA and OSHA.
[b]Proportion of rats developing nasal cavity squamous cell carcinoma.

FIGURE 2

Substantial differences between the values of the fitted multistage model and its 95% upper confidence limits . . .[a]

. . . Absolute differences



. . . Relative differences

Dose (ppm)	95% Upper confidence limit / Fitted model value
5.6	2
2.0	41
1.0	368
0.5	3,140
0.1	417,000
0.01	423,000,000

[a]On risk caused by the independence of high- and low-dose behavior in the structure of the multistage model.

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In order to obtain more useful quantitative dose-response assessments, the plethora of simplistic models must be replaced by more biologically reflective dose-response models that utilize the available scientific information. New dose-response modeling techniques can incorporate representations of the exposure in terms of dose scales based on cell turnover rates, repair processes, immune system responses, and physiological and pharmacokinetic models of the absorption, delivery, metabolism, and elimination of chemicals.

These new techniques can incorporate distributions of individual background exposure levels and individual susceptibilities to low levels of a chemical. They also can incorporate such factors as low-dose linearity on a biologically relevant scale; age-dependent changes in the number of target cells and time-dependent effects of cell proliferation on the number of intermediate cells in a multistage process; and dose levels, susceptibilities, and background exposures that are not necessarily constant over time. These new, more biologically reflective models are now described as state-of-the-art, and additional research should lead to even better dose-response models.

Relevant dose scales

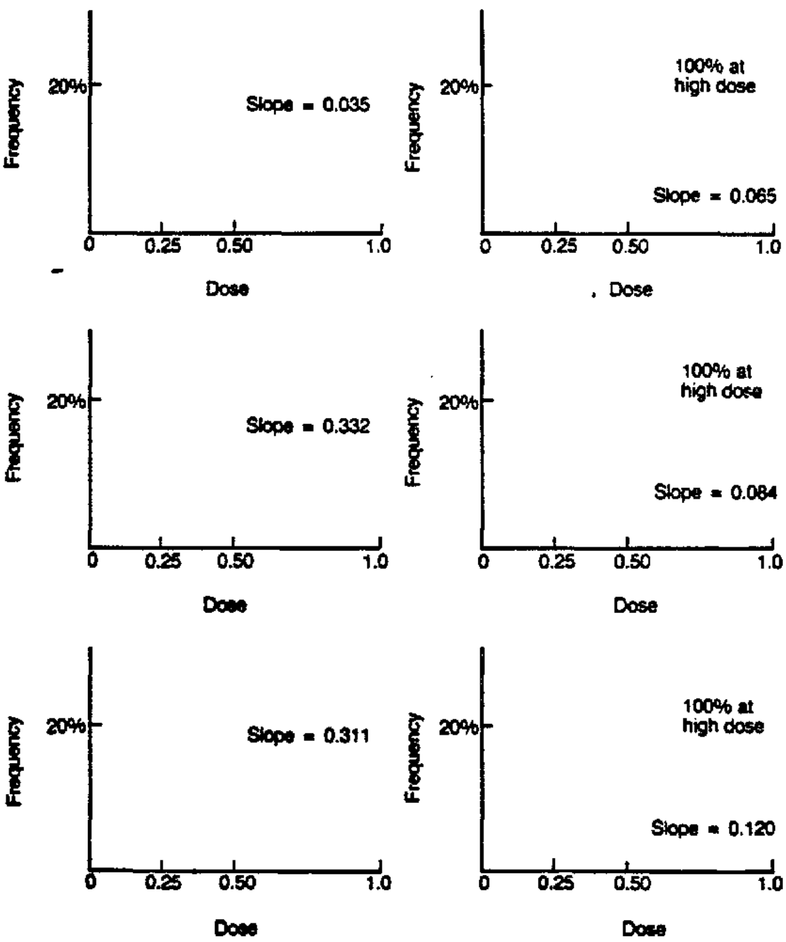
The dose level should be expressed on a biologically relevant scale. For example, Figure 4 shows that the dose level corresponding to an inhalation exposure can be expressed in several terms: the concentration of the chemical in the air inhaled; the total amount of the chemical inhaled over time; the amount of the chemical or its active metabolite reaching the target cells of a particular tissue; and the amount of chemical or metabolite interaction with DNA or the amount of cell damage that escapes repair.

The dose scale can be expressed as the administered dose, the intermediate dose, the dose delivered to the target site, or the biologically effective dose. The biologically effective dose reflects not only the amount of the chemical or metabolite delivered to the target site but also the net generation of cancer-related activity, including cell turnover, DNA repair, and immune system responses.

There are advantages to studying biological response. Using a biologically reflective dose instead of the administered dose, the modeler can incorporate known biology, physiology, and pharmacokinetics. This reduces the uncertainty and the number of unknowns in the dose-response model and aids extrapolations from high doses to low doses, from species to species, from one exposure route to another, and from one exposure time frame to another.

If there is insufficient scientific knowledge to establish the complete transformation from administered dose to a biologically effective dose, then using even a partial transformation or best approximation based on what is known should lead to a better risk assessment than using only the administered dose.

FIGURE 3
Nonresponsiveness of current potency measures to experimental data with the linearized multistage model[a,b]



[a]The potency measure currently used by the U.S. EPA equals the slope of the linearized multistage model in the lower dose region. Here the slope is evaluated for Dose = 0.1. The observed response frequencies are indicated by the large dot and correspond to an experiment with 50 subjects at each dose level.
[b]Six experimental outcomes with very different dose-response relationships. The largest of the six corresponding potency measures differs from the smallest by less than one order of magnitude

Individual susceptibilities

Individuals vary in their responses to a particular exposure to a potentially hazardous chemical. Individual variation is influenced by many factors, including variation in background exposures, genetic traits, preexisting diseases, and behavioral traits (*1*). An extension of the linear multistage model utilizes the biologically effective dose and reflects individual variations in background exposure and biological susceptibility to low levels of a chemical. An analogous extension of a more biologically motivated model that emphasizes the multistage carcinogenic process, age-dependence, and cell proliferation is described below.

The background exposure for a population of individuals, D_0, is a random variable; that is, the level of exposure from all sources, other than the one source being regulated, is potentially different for different members of the population. Each individual has his own particular value d_0 for the background dose D_0.

An animal's background exposure is dependent upon such factors as environment and diet. A human's d_0 can depend on these same factors as well as occupation, lifestyle, and hygiene.

Similarly, because there is often interindividual variation in biological factors such as metabolic rates and enzyme

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levels, the biological susceptibility S to a particular chemical varies in a population from one individual to another. For a population, S is a random variable, and each individual has a particular value s for the susceptibility S.

An Individualized Response Model utilizes the biologically effective dose as the dose scale for dose–response modeling and reflects the interindividual variation in the susceptibility S and the background dose D_0. A description of how the Individualized Response Model works is provided in the box. Figure 5 provides an overview of the components and structure of the model.

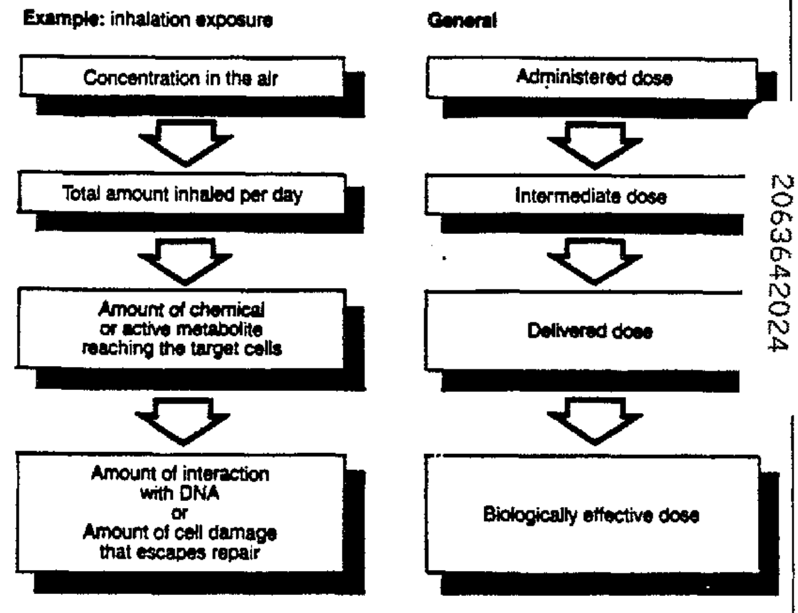
A reasonable approximation for the distribution of the background dose D_0 in the population may often be the lognormal distribution. There has been considerable historic success in using the lognormal distribution to represent the distributions of a wide variety of exposures and biological phenomena. Lognormal distributions agree with $D_0 > 0$. In addition, lognormal distributions can be very skewed to match chemical carcinogens for which D_0 is usually very near zero. On the other hand, lognormal distributions can be nearly symmetrical and more like the normal distribution if D_0 is frequently moderately large. Similarly, the distribution of the susceptibility S may be approximated by a lognormal distribution.

The biological phenomena represented by susceptibility and the way in which susceptibility enters into the carcinogenic process will generally be different for different chemicals. Sometimes susceptibility can be expressed through a susceptibility frontier. The delivered dose corresponding to the transition from substantially lowered carcinogenic effectiveness to the dose region where the predominant mechanism resisting or suppressing carcinogenesis is overwhelmed is the susceptibility frontier.

For a population of individuals, the susceptibility frontier F is a random variable. Each individual has his or her own particular value f for the susceptibility frontier F. Genetic differences in metabolic activation and detoxification, tissue sensitivity, repair efficiency, and immune system responses contribute to the individual variation in the value of the susceptibility frontier (2, 3).

A susceptibility frontier is different from a tolerance. If the delivered dose becomes greater than an individual's tolerance, then cancer is a certainty; however, as the delivered dose becomes greater than the individual's susceptibility frontier, then the individual's cancer probability increases more rapidly but doesn't immediately become a certainty.

FIGURE 4
Modeling with more biologically relevant dose scales
Quantifying the dose level



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The concept of a susceptibility frontier is also different from that of a threshold. A threshold denotes a dose level below which absolutely no carcinogenesis is possible, whereas a susceptibility frontier indicates only a transition from the normal functioning of the body's carcinogenic defense mechanisms to dose levels overwhelming those mechanisms. Also, a threshold is the same for every member of the population, whereas the susceptibility frontier differs for each individual.

The concept of a susceptibility frontier can be illustrated in simple terms as follows: Suppose that for a particular individual a chemical exposure causes a particular number of specific molecules to reach and invade a target cell. Also, suppose that the target cells have, for simplicity, a single cancer defense mechanism relative to these invaders—say a detoxification process—and that the cell begins with 20 opportunities to carry out the detoxification of an invading molecule. However, at each opportunity the probability of detoxifying an invader is, for example, only 0.9 (not 1.0), and a successful detoxification reduces the number of detoxification opportunities the next invader must face by one. In such circumstances the expected number of invaders that avoid random detoxification can be shown to be approximately $1 \times 10^{-(21-X)}$ if there are X invaders and $X \leq 20$, and $X - 20$ if there are X invaders and $X > 20$.

If the probability of a carcinogenic response is proportional to the number of invaders that avoid detoxification, then the probability of a carcinogenic response undergoes an exponential increase (nearly linear at very low doses and slow overall) as the delivered dose of the chemical increases until it generates approximately 20 invaders. At this point further increases in the delivered dose correspond to more rapid linear increases in the probability of a carcinogenic response.

In this example the delivered dose level corresponding to the generation of 20 invaders would be called the individual's susceptibility frontier f. In general, if an individual has a nonzero susceptibility frontier, then f occurs at the point where, as the dose increases, the effective dose shifts from a slowly increasing function of the delivered dose to a more rapidly increasing linear function of the delivered dose.

One form of the Individualized Response Model corresponds to a multistage model, which is linear in the biologically effective dose.

Mathematically,

$$P[t; BED(d,d_0,f)] = 1 - \exp[-\alpha_0 - \alpha_1 \times BED(d,d_0,f)]$$

when the susceptibility S is the susceptibility frontier F, and f is the value of F. The greek constants α_0 and α_1 would usually be estimated from the chronic dose–response data.

The functional form of the biologically effective dose, $BED(d,d_0,f)$, would be determined on the basis of scientific research ancillary to the response frequency tabulation in chronic bioassays. Alternatively, the functional

How the Individualized Response Model works

In an Individualized Response Model the proportion $Pr(t;d)$ of the entire population at risk that is expected to develop a specified carcinogenic response, in the absence of competing mortality, by time t for an administered dose d is the weighted average of

$P[t; BED(d,d_0,s)]$ = dose-response model in terms of the biologically effective dose $BED(d,d_0,s)$;

where the weights reflect the proportion of the population that have a susceptibility S equal to s and a background dose D equal to d_0.

Herein, $P[t; BED(d,d_0,s)]$ denotes the probability of the specified response occurring by time t, in the absence of competing mortality, for the particular biologically effective dose $BED(d,d_0,s)$ that arises when the administered dose is d, the random background dose D_0 takes on the value d_0, and the random susceptibility S takes on the value s. Figure 5 provides an overview of the components and structure of an Individualized Reponse Model.

form of the biologically effective dose is estimated during the fitting of the chronic dose-response data. The estimated biologically effective dose could increase linearly with the delivered dose for delivered doses exceeding the susceptibility frontier and increase exponentially (with associated low-dose linearity) for delivered doses less than the susceptibility frontier.

Modeling through time

The Individualized Response Model's probability that a randomly selected individual from the population will have a specified carcinogenic response by time t for an administered dose d_0 is the expectation of $P[t; BED(d,d_0,s)]$ with respect to the distribution of the background dose D_0 and the susceptibility S in the population. The relationship, $P[t; BED(d,d_0,s)]$, between the likelihood of a response by time t and the biologically effective dose $BED(d,d_0,s)$ for given values of d_0 for D_0 and of s for S, is averaged in the Individualized Response Model. This model can be a better, more complete reflection of the available scientific information on the carcinogenic risk associated with a specific situation if the dynamic nature of the biological processes involved is explicitly reflected in $P[t; BED(d,d_0,s)]$.

By modeling the progression of the biological system through time, $P[t; BED(d,d_0,s)]$ can reflect explicitly not only the different stages in the carcinogenic process, but also cell proliferation, biological processes that are age-dependent, and doses that are not constant over time. Such models allow risk to be characterized in terms that reflect how the probability of a carcinogenic response changes with time.

In the multistage theory of carcinogenesis, a carcinogenic response occurs when k successive events stemming from a single cell have occurred (*4*). In this context, $P[t; BED(d,d_0,s)]$ is determined by the rates at which the number of cells completing successive events increase over time. Figure 6 provides mathematical details for the general k-stage carcinogenic process.

Conceptually, the probability $P[t; BED(d,d_0,s)]$ arises in a very natural way. For example, if the carcinogenic process involves two stages, then the process involves normal stem cells, intermediate cells that have undergone the first of the two carcinogenic events, and malignant cells that arise from intermediate cells by undergoing the second carcinogenic event. Malignant cells are assumed to produce the specified carcinogenic response.

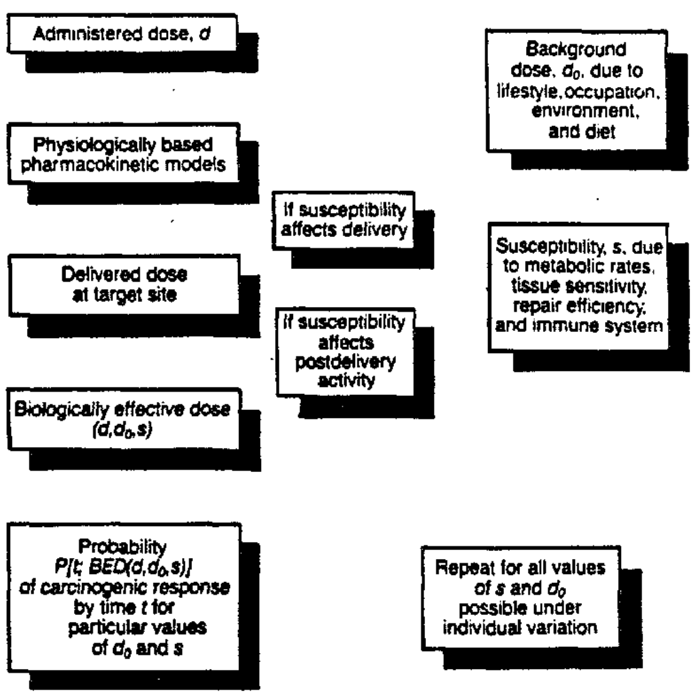
The number of malignant cells that arise at a particular time equals the rate at which an intermediate cell gives rise to malignant cells at that time multiplied by the total number of intermediate cells alive at that time. The total number of intermediate cells at a particular time, say T, depends primarily on the number of intermediate cells that arise from normal stem cells at a time T' prior to T and the net growth in that number of intermediate cells due to cell birth and death between T' and T.

The number of intermediate cells that arises from normal stem cells at a particular time is the rate at which a normal stem cell gives rise to intermediate cells at that time multiplied by the total number of normal stem cells alive at that time.

The entire carcinogenic process and its components are all tracked through time. That is, the number of cells in each stage, the transition rates from stage to stage, and the net within-stage proliferation rates due to cell birth (replication) and death or terminal differentiation are evaluated explicitly at each point in time.

Thus the dependence of these factors on time and the biologically effective dose at that time can be explicitly incorporated. Because the biologically effective dose is calculated at each time, time-dependent changes in the administered dose, the background dose, and

FIGURE 5
Individualized Response Model: components and structure



$Pr(t;d)$ = Weighted average of $P[t; BED(d,d_0,s)]$, where the weights reflect the likelihood of the particular values of d_0 and s
= Probability of a carcinogenic response by time t in an individual randomly selected from the population

the susceptibility can also be incorporated.

Other models are special cases of the form for $P[t;\ BED(d,d_0,s)]$ shown in Figure 6 (5–7). These other models assume that the background dose D_0 and the susceptibility S have the same values for every individual and that the susceptibility frontier F is zero for every individual.

Benefits

There are several substantial benefits to using the Individualized Response Model. By explicitly including the interindividual variation in susceptibility and background dose, quantitative risk assessment can more accurately reflect the population at risk. Particular distributions of susceptibility and background doses within the population can be studied and directly incorporated into the model. This removes some of the unreasonable elements present in most quantitative risk assessments, namely, the assumption that everyone in the population is as sensitive as the most sensitive individual.

The model uses dose on the most relevant scale—the biologically effective dose scale—and incorporates changes in the dose over time. Physiological and pharmacokinetic research can be used to provide information on the delivered dose corresponding to a particular route of exposure, the interaction of administered and background doses, and any effects of susceptibility on the delivery process.

Molecular biology and a careful analysis of a chemical's mechanistic behavior can establish the nature of intracellular susceptibility and the presence or absence of a susceptibility frontier. Such research can also indicate which phenomena are age-dependent and the functional form of such dependencies. Much of this dosimetry may either be already available or obtainable from short-term experiments (8).

Furthermore, the number and range of nonzero dose levels for which the biologically effective dose is obtainable are generally much greater than the few experimental dose levels considered in a chronic bioassay. Hence, the relationship between the administered dose and the biologically effective dose should be obtainable over a wide range of administered doses, and the biologically effective dose corresponding to the actual exposure levels of interest can be more reasonably determined.

In addition, the research results concerning the likely functional dependence of the dose-response model parameters on the dose assume that the dose is expressed on the biologically effective dose scale. The use of the biologically effective dose should reduce the uncertainty in the high- to low-dose extrapolation portion of quantitative risk assessment.

By incorporating modeling through time, the dose-response relationship for a given biologically effective dose can be more biologically motivated. Such modeling allows $P[t;\ BED(d,d_0,s)]$ for given $BED(d,d_0,s)$ to be analyzed in biologically meaningful terms, reflecting both the qualitative and quantitative mechanistic information generated by the biologist and the toxicologist.

For example, Thorslund et al. (7) suggest a correspondence between modes of action in a two-stage (k=2) carcinogenic process and the parameters shown in the Figure 6. (See box.)

Such studies would allow the model structure and issues such as linearity versus nonlinearity to be determined by scientific inquiry rather than by assumption or policy. The ability to incorporate supplementary scientific investigations should promote increased data acquisition, provide broader scientific participation in quantitative risk assess-

FIGURE 6
Mathematics of the Individualized Response Model*

Tracing the evolution from stage (0) cells (normal stem cells) to stage (k) cells (malignant cells)

$C_0[t_1, BED]$ = Number of stage (0) cells (normal stem cells) at time t_1

$C_1[t_2, BED]$ = Number of stage (1) cells at time t_2

$$= \int_0^{t_2} M_0[t_1, BED(t_1)] \times C_0[t_1, BED] \times \exp\{\int_{t_1}^{t_2} G_1[v, BED(v)]dv\}dt_1$$

$M_0[t_1, BED(t_1)] \times C_0[t_1, BED]$ = Number of stage (0) cells which undergo the transformation to stage (1) cells at time t_1

$\exp\{\int_{t_1}^{t_2} G_1[v, BED(v)]dv\}$ = Number of stage (1) cells at time t_2 arising from a single stage (1) cell that came into being at time t_1.

$C_{k-1}[t_k, BED]$ = Number of stage ($k-1$) cells at time t_k

$$= \int_0^{t_k} M_{k-2}[t_{k-1}, BED(t_{k-1})] \times C_{k-2}[t_{k-1}, BED] \times \exp\{\int_{t_{k-1}}^{t_k} G_{k-1}[v, BED(v)]dv\}dt_{k-1}$$

$M_{k-1}[t_{k-1}, BED(t_{k-1})] \times C_{k-2}[t_{k-1}, BED]$ = Number of stage ($k-2$) cells that undergo the transformation to stage ($k-1$) cells at time t_{k-1}

$\exp\{\int_{t_{k-1}}^{t_k} G_{k-1}[v, BED(v)]dv\}$ = Number of stage (k-1) cells at time t_k arising from a single stage (k-1) cell that came into being at time t_{k-1}

$M_{k-1}[t_k, BED(t_k)] \times C_{k-1}[t_k, BED]$ = rate of formation of stage (k) cells, i.e., rate of malignant cell formation

$$P[t;\ BED(d,d_0,s)] = 1.0 - \exp\{-\int_0^{t-w} M_{k-1}[t_k, BED(t_k)] \times C_{k-1}[t_k, BED]dt_k\}$$

= Cumulative effect of the rate of malignant cell formation for all times up to the last time (t-w) which could produce the specified carcinogenic response by time t

Components of $P[t;BED(d,d_0,s)]$:

$d(T)$	= administered dose at time T
$d_0(T)$	= background dose at time T; a function of the base value d_0 and the effect of time on that base value
$s(T)$	= susceptibility at time T; a function of the base value s and the effect of time on that base value
$BED(T)$	= $BED[d(T), d_0(T), s(T)]$ = biologically effective dose at time T; reflects the interrelationship between $d(T)$, $d_0(T)$, and $s(T)$
$C_i[T, BED]$	= the number of stage (i) cells at time T, i = 0, 1, 2, ... k-1; a function of the time T and the biologically effective dose levels between time zero and time T
$M_i[T, BED(T)]$	= rate per unit time per cell of cell transformation from stage (i) to stage (i + 1), i = 0, 1, 2, ... k-1; a function of the time T and the biologically effective dose at that time
$G_i[T, BED(T)]$	= growth rate per unit time per cell of number of stage (i) cells, net effect of cell births and deaths (including terminal differentiation), i = 1, 2, ... k-1; a function of the time T and the biologically effective dose at that time
w	= the amount of time for a malignant cell to become the specified carcinogenic response (a detectable tumor, death from tumor, etc.)

*The relationship $P[t;\ BED(d,d_0,s)]$ between response frequency and biologically effective dose $BED(d,d_0,s)$ for particular values d_0 and s of background dose D_0 and susceptibility S when carcinogenesis is modeled through time and represented as a k-stage biological process.

Correspondence between modes of action* and parameters in Figure 6

- Cocarcinogens, which induce regenerative hyperplasia as the normal consequence of a tissue's attempt to repair toxic damage, affect C_0;
- Initiators, which induce mutation, oncogene activation, or chromosomal translocation, affect M_0;
- Promoters, which increase the number of transformed preneoplastic cells through clonal expansion, affect G_1;
- Completers, which increase the rate of transformation from the penultimate stage to a malignant cell, affect M_1;
- Inhibitors, which reduce the rate of transformation to malignancy by different mechanisms, cause decreases in C_0, M_0, M_1, or G_1.

Because the model uses biologically meaningful parameters, its time- and dose-dependence may be investigated in special studies supplemental to the collection of response frequencies in chronic bioassays.

*In a two-stage ($k=2$) carcinogenic process.

ment, and instill greater confidence in the results.

Some of the greatest benefits of the new modeling occur when the human risk characterization involves extrapolation. Modeling with biologically defined components permits the identified differences between species, exposure routes, and exposure time frames (chronic, short-term, and only adult years) to be explicitly incorporated into the model.

The functional form of the particular components where differences do occur, such as the biologically effective dose and the number of normal stem cells (C_0), can be updated to reflect the new situation. Also, the distributions of background dose and susceptibility for the new situation can replace the old distributions.

Individualized Response Models can incorporate new results on the individual components of the dose-response model and utilize the specific functional forms of these components for particular situations. Thus these new models provide human risk characterizations that are more up-to-date, accurate, and pertinent to the particular exposure situations being evaluated.

Prognosis

Quantitative cancer dose-response modeling is the subject of intensive research. New dose-response models can incorporate research on more biologically relevant dose scales. The new models still involve some simplifying assumptions and are not exact biological models; however, the extensions described make it possible to incorporate more of the current scientific understanding of carcinogenesis and more biological reality.

These more complete biologically based models provide more accurate and informative quantitative risk assessments to both the public and risk managers. Furthermore, the new models may inspire research directions that will yield the experimental data needed to more accurately determine the dose-response relationship for a particular carcinogen. The new capabilities for dose-response modeling and an expanding data base provide the potential for substantial improvements in quantitative cancer risk assessment.

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